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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,233	MARTUZA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 9-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 9-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/31/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 05/13/2008 has been entered. Claims 1-6 and 8 are cancelled. Claims 7 and 9-18 are pending. Claims 7, 9, and 10 are amended. Claims 7 and 9-18 are currently under examination.

This application 10/748,233 filed on 12/31/2003 is a divisional of Ser. No. 09/625,509, filed July 25, 2000, now U.S. Pat. No. 6,699,468, which is a divisional of Ser. No. 09/004,511, filed Jan. 8, 1998, which is a continuation of U.S. patent application Ser. No. 08/478,800, filed Jun. 7, 1995, now abandoned, which is a continuation of U.S. Ser. No. 08/264,581 filed Jun. 23, 1994, now U.S. Pat. No. 5,585,096.

It is noted that the claim identifier of claim 9 filed on 05/13/2008 should be "Currently Amended" instead of "Previously Presented". This is considered as a non-compliance amendment (37 CFR 1.121, MPEP § 714). However, as Applicant's remark filed on 05/13/2008 clearly indicates that claim 9 has been amended and the incorrectly marked claim identifier of claim 9 does not interfere with examination of the claim, the examination proceeds to facilitate the prosecution of the application.

Claim Objection

1. Previous objection of claims 7 and 9-18 because the limitation in line 3 of claim 7 "and the ribonucleotide reductase gene should read "and *in* the ribonucleotide reductase gene" or "in each of the gamma34.5 and ribonucleotide reductase genes", is ***withdrawn*** because the claim has been amended.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 7 and 9-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendment filed on 05/13/2008.*

Claim 7 recites the limitation "the mutations" in "wherein the mutations result in a lack of function of each gene product" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 9-18 depend from claim 7.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7, 9-18 **remain** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response in a tumor cell and (ii) that is altered in the gamma34.5 gene and in the ribonucleotide reductase gene such that no functional gamma34.5 gene or ribonucleotide reductase gene product is made, wherein the neurovirulence of said herpes simplex virus is

attenuated and said herpes simplex virus and is capable of replication in dividing cells, but not in non-dividing cells, **does not** reasonably provide enablement for a herpes simplex virus with a genome comprising 1) any alteration in the gamma34.5 or ribonucleotide reductase genes other than an alteration that results in a lack of function of each gene product, or 2) for a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence and the effect of having the ability to replicate in dividing cells and not in non-dividing cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
Applicant's arguments filed 05/13/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-10 of the office action mailed on 01/24/2008.

It is noted that the third aspect of the rejection documented on page 5 of the office action mailed on 01/24/2008 pertaining to non-enabled embodiment of a HSV viral vector comprising expressible non-herpes simplex virus nucleotide sequence encoding *any* desired protein for eliciting an immune response in a tumor cell, is withdrawn because the claim amendments filed on 05/13/2008 have limited to nucleotide sequence encoding a cytokine.

Applicant's Arguments

Applicant argues that claim 7 has been amended to specify that the desired protein is a cytokine that is capable of eliciting immune response in a tumor cell and that the mutations result in a lack of function of each gene product of the gamma34.5 gene and the ribonucleotide

reductase gene. Applicant indicates that these revisions are supported by the specification (see the published application, e.g. at page 2, paragraph [0019]; and at page 6, paragraph [0077]) and in line with the Examiner's recommendation (Office Action, the paragraph bridging pages 4 and 5). Applicant indicates that the specification further discloses construction of HSV vectors and impairment of gamma34.5 and ribonucleotide reductase gene expressions (published application, pages 4 and 5). Therefore, Applicant argues that one skilled in the art is enabled by the teachings of the specification to make the claimed HSV mutant.

Responses to Applicant's Arguments

As noted above, the aspect of the rejection pertaining to a HSV viral vector comprising expressible non-herpes simplex virus nucleotide sequence encoding *any* desired protein for eliciting an immune response in a tumor cell, has been withdrawn because of the claim amendments filed on 05/13/2008.

However, as documented in the preceding section of rejection of claims 7 and 9-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amendments of claim 7 reciting the limitation "wherein the mutations result in a lack of function of each gene product" lacks antecedent basis. Accordingly, the amended claim 7 continues to read on any alteration of gamma34.5 gene and RR gene because the claim as written, there is no nexus between the altered gamma34.5 gene and the RR gene, and the mutations, as recited in amended claim 7. In other words, the amended claim 7 as written does not limit the altered gamma34.5 gene and the RR gene to null mutations of both gamma34.5 gene and the RR gene. Furthermore,

it is noted that Applicant's response filed on 05/13/2008 does not address the second non-enabled embodiment regarding a viral particle exhibiting any effect/phenotype from the alteration other than attenuation of neurovirulence (due to null mutation of gamma34.5) and the effect of having the growth advantage in dividing cells over in non-dividing cells (due to null mutation in ribonucleotide reductase gene).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Previous rejection of claims 7, 9-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991), is ***withdrawn*** because the claims have been amended.

Claim 7 has been amended to read as follows: A herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) that is altered in the □34.5 gene and in the ribonucleotide reductase gene, wherein the mutations result in a lack of function of each gene product.

Neither Roizman et al. nor Chang et al. teaches a HSV comprising an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine.

5. Previous rejection of claim 14-16 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991) as applied to claim 13 above, and further in view of McKay et al. (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and Wright, Jr. (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994), is ***withdrawn*** because the claims have been amended.

Claim 7 has been amended to read as follows: A herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) that is altered in the □34.5 gene and in the ribonucleotide reductase gene, wherein the mutations result in a lack of function of each gene product.

None of Roizman et al., Chang et al., McKay et al., and Wright, Jr. teaches a HSV comprising an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine.

6. Claims 7, 9-13, 17 and 18 are newly rejected as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Chang et al.** (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991) and **Vile et al.** (Vile

RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994). This rejection was previously applied to claim 8 (see p. 14 of the Office action mailed 1/24/08). *This rejection, over claims 7, 9-13, 17 and 18, is necessitated by claim amendments filed on 05/13/2008.*

Independent claim 7 has been amended to read as follows: A herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) that is altered in the □34.5 gene and in the ribonucleotide reductase gene, wherein the mutations result in a lack of function of each gene product.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in claim 7 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. Additionally, because this is an inherent property of the cytokine, any art teaching a cytokine would necessarily be capable of eliciting an immune response against a tumor cell. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). It is noted that in the art G207, as recited in claim 10 of instant application, is the name of an HSV that contains deletions of both copies of the gamma34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

Roizman et al. teaches the following: **(i)** The function of the gene gamma34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001). **(ii)** The use of the HSV-1 virus with a specific mutation in the gamma34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "gamma34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the gamma34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the gamma34.5 gene placed under a suitable target specific promoter (which reads on claims 13 and 17 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001).

Roizman et al., do not teach (1) a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene, and (2) a herpes simplex virus with a genome that expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell.

Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that

ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial lacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir, hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of *a foreign gene* into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Vile et al. teaches that (i) transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), and (ii) constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994), and that (iii) use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roizman et al. (2001) regarding the characteristics of a mutant herpes simplex virus comprising a disrupted gamma34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, with the teachings of Chang et al. (1991) regarding the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, and with the teachings of Vile et al. (1994) regarding exogenous expression of a cytokine gene results in diminishment or elimination of tumorigenicity of tumor cells via elicitation of immune response to arrive at the claimed HSV with disrupted both gamma34.5 and ribonucleotide reductase (RR) gene that exhibits no neurovirulence, and specifically targeting to fast dividing cancer cells, and expressing a cytokine gene that elicit an immune response against a tumor cell, as recited in claims 7, 9-13, 17 and 18 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Chang et al., and Vile et al. (1994) because combination of the gamma34.5 and RR gene mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells harming healthy cells, as taught by Chang et al. (See first paragraph, left column, page 438, Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6delta strain, results in severe growth impairment in non-dividing cells), and furthermore, the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

There would have been a reasonable expectation of success given (1) the demonstration that the "gamma34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, and (2) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991, and (3) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. Applicant argues that the combination of Roizman et al., Chang et al. and Vile et al. is based on "obvious to try" rational that is improper under the statute and governing case law. In this regard, Applicant cites the U.S. Supreme Court's decision, KSR International Co. v. Teleflex Inc., and EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. § 103..., published in the Federal Registrar, Vol. 72, No. 195 (October 10, 2007) as support. Applicant argues that the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness because, contrary to the Examiner's contention, there was no reasonable expectation of success in view of the state of art at the time of filing. Applicant

argues that the contemporaneous art was hardly one characterized by "a finite number of identified, predictable potential solutions to the recognized ... problem," namely, the treatment of malignant tumors, and to the contrary, the skilled artisan would have encountered panoply of co-treatments that might be combinable with oncolytic HSV. Applicant argues that as the accompanying Rule 132 declaration of inventor Samuel Rabkin demonstrates, moreover, the prior art was replete with publications evidencing a contemporaneous understanding in the field that cytokines, such as IL-1□, IL-2, IL-3, TNF, INF-α, IFN-β, INF-γ, M-CSF-1 and GM-CSF, ***protect*** a host from HSV infection and ***diminish*** replication of HSV in the host cells. Applicant indicates that as Dr. Rabkin attests, this conventional wisdom of the day would have led the skilled artisan away from expressing cytokines in the replication competent HSV for purposes of tumor therapy, as presently claimed, since therapy with such mutant HSV requires HSV to infect and replicate in tumor cells of the host, in order to kill tumor cells. Applicant indicates that further alteration of such mutant HSV to express cytokines is done to elicit an immune response against the tumor cell, enhanced by cell killing due to the HSV infection. Id. at page 6, paragraph [0077]. Applicant argues that, the skilled artisan would have expected that expression of a cytokine to protect the cells from HSV infection and replication, which would diminish the therapeutic effect of the claimed, replication-competent HSV, and by the same token, the skilled artisan would not have expected, as the Examiner contends, that combining cytokines with the mutant HSV might result in an enhanced tumor therapy.

Responses to Applicant's Arguments

With regard to the scientific aspect of Applicant's arguments that cytokines, such as IL-1□, IL-2, IL-3, TNF, INF-α, IFN-β, INF-γ, M-CSF-1 and GM-CSF, protect a host from HSV infection and diminish replication of HSV in the host cells, the Examiner agrees in general with the declaration by Dr. Rabkin, and the references cited therein, with regard to the biological functions of a cytokine in protecting a host from herpes simplex virus (HSV) infection and in preventing HSV replication in the host. It is noted that Applicant's arguments are applicable as to endogenous expression of cytokine (i.e. pre-existing cytokine before virulent HSV infection) as part of immune system that can prevent virulent HSV infection. Nevertheless, the claims are directed to expressing a cytokine gene from a mutated HSV vector which is non-neurovirulent and replicates primarily, if not exclusively, in fast dividing tumor cells. In this setting, the cytokine gene is incorporated into the mutated HSV genome and will be expressed only after claimed mutated HSV vector infect targeted tumor cells. Therefore, Applicant's arguments pertaining to the general immune protective effect of cytokine expression in preventing virulent HSV infection have been fully considered and found not persuasive. Furthermore, Vile et al. clearly states that transduction of tumor cells with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity of tumor cells (See first sentence of Introduction, page S59, Vile et al., 1994).

With regard to the legal aspect of Applicant's arguments that "obvious to try" rational that is improper under the statute and governing case law because the skilled artisan would have encountered a panoply of co-treatments (which Applicant asserts it's not a finite number) that might be combinable with oncolytic HSV, the Examiner notes that, as cited above, Vile et al. clearly states that transduction of tumor cells with cDNA encoding various cytokines and/or

immune accessory molecules has been shown to diminish or eliminate tumorigenicity of tumor cells (See first sentence of Introduction, page S59, Vile et al., 1994) and constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See conclusions, right column, second paragraph, Vile et al., 1994). The teachings by Vile et al. provide strong motivation for a skilled artisan to combine the anti-tumor effect of cytokine taught by Vile et al. to be expressed from the non-pathogenic HSV vector specifically targets to tumor cells by the combined teachings of Roizman et al. and Chang et al. Therefore, Applicant's arguments regarding the assertion that combining the teachings of Roizman et al., Chang et al, and Vile et al. being based on an "obvious to try" rational with infinite number to be identified, have been fully considered and found not persuasive.

7. Claims 14-16 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Chang et al.** (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991) and **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claim 7, 9-13, 17 and 18 above, and further in view of **McKay et al.** (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and **Wright, Jr.** (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994). *This rejection is necessitated by claim amendments filed on 05/13/2008.*

Independent claim 7 has been amended to read as follows: A herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) that is altered in the gamma34.5 gene and in the ribonucleotide reductase gene, wherein the mutations result in a lack of function of each gene product.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in claim 7 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. It is noted that in the art G207, as recited in claim 10 of instant application, is the name of an HSV that contains deletions of both copies of the gamma34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

The teachings of Roizman, Chang et al. and Vile et al. have been discussed in the preceding rejection of claims 7, 9-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Chang et al. 1991 and Vile et al. (1994).

However, the combined teachings of Roizman et al., Chang et al., and Vile et al. do not teach a herpes simplex virus with a genome that expresses a exogenous gene, targeting to a specific tumor type with a tumor cell specific promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, epidermal growth factor (EGF) promoter, as recited in claims 14-16 of instant application.

At the time of filing of instant application, it is known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor

specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, Jr. 1997 teaches the tumor tissue specific expression of bFGF, EGF driven by their endogenous promoters can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH), indicating that the promoters of bFGF, EGF genes are tumor specific with respect to its regulation (See title and lines 30-36. column 2, Wright et al., 1997).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a non-HSV nucleotide sequences encoding a cytokine under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., in the herpes simplex virus (HSV) vector bearing disrupted both gamma 34.5 and ribonucleotide reductase genes that exhibits no neurovirulence and specifically targeting to fast dividing cancer cells, and the HSV vector expresses exogenous cytokine gene resulting in elicitation of immune response for against a tumor cell, by the combined teachings of Roizman et al. (2001), Chang et al. (1991), and Vile et al. (1994).

It would have been obvious at the time of filing to combine the teachings of Roizman et al. (2001), Chang et al. (1991), and Vile et al. (1994) on a HSV vector for cancer treatment with the expression of a non-HSV nucleotide sequences encoding a cytokine under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., to arrive at the claimed herpes simplex viruses as recited in claims 14-16 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer to introduce the expression of a non-HSV nucleotide sequences encoding a cytokine by combined teachings of Roizman 2001, Chang 1999, and Vile et al., wherein the cytokine expression is under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., because the HSV vector is non-pathogenic and specifically targeting to fast dividing tumor cells without harming healthy cells, and the non-HSV nucleotide sequences encoding a cytokine only expresses the cytokine in tumor cells resulting in elimination or diminishment of tumor cells.

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al., Chang et al. and Vile et al. being non-pathogenic and specifically targeting to fast dividing tumor cells, and expressing a cytokine, and (2) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 7, 9-13, 17 and 18 as being unpatentable over Roizman et al. in view of Chang et al. and Vile et al.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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